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Patentanmeldung Nr. **Patent application No.** **Demande de brevet n°**

02292736.2

PRIORITY DOCUMENT

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R C van Dijk

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SUEDE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Quinazoline derivatives

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QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example pp60$^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example pp60$^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification

includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, are frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer

(Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

We have now found that surprisingly certain quinazoline derivatives possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of the Src family of non-receptor tyrosine kinases, for example by inhibition of one or more of c-Src, c-Yes and c-Fyn.

It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702; Boyce *et al.*, J. Clin. Invest., 1992, 90, 1622-1627; Yoneda *et al.*, J. Clin. Invest., 1993, 91, 2791-2795 and Missbach *et al.*, Bone, 1999, 24 , 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

The compounds of the present invention are also useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory diseases (for example rheumatoid arthritis and inflammatory bowel disease), fibrotic diseases (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, blood vessel diseases (for example atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

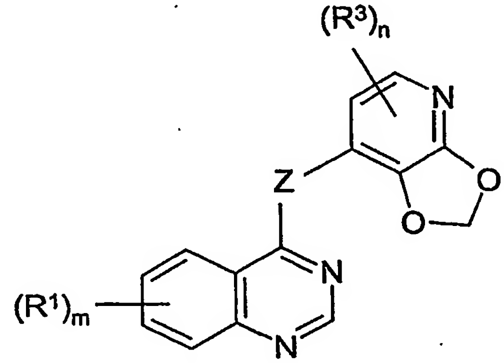
Generally the compounds of the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase. Furthermore, certain compounds of the present invention possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against VEGF receptor tyrosine kinase. Such compounds possess sufficient potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, that they may be used in an amount sufficient to inhibit, for example, c-Src and/or c-Yes whilst demonstrating little activity against VEGF receptor tyrosine kinase.

It is stated in International Patent Application WO 01/94341 that a range of quinazoline derivatives are useful in the treatment of cancer. The compounds are stated to possess inhibitory activity against the Src family of non-receptor tyrosine kinases. There is the disclosure therein of certain 5-substituted quinazoline derivatives including certain 5-substituted 4-(2,3-methylenedioxyanilino)quinazolines. There is no disclosure therein of any 4-(2,3-methylenedioxypyrid-4-ylamino)quinazoline derivatives.

It is stated in International Patent Application WO 02/16352 that a range of 4-(2,3-methylenedioxyanilino)quinazoline derivatives are useful in the treatment of cancer.

The compounds are stated to possess inhibitory activity against the Src family of non-receptor tyrosine kinases. There is no disclosure therein of any 4-(2,3-methylenedioxypyrid-4-ylamino)quinazoline derivatives.

According to one aspect of the invention there is provided a quinazoline derivative of the Formula I



I

wherein **Z** is an O, S, SO, SO_2 or $C(R^2)_2$ group wherein each R^2 group, which may be the same or different, is hydrogen or (1-6C)alkyl;

m is 0, 1, 2 or 3;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2 - X^2 -$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^3 - Q^3$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl,

(2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino and (1-3C)alkylenedioxy, or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and N(R^9), wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, N(R^{10}) and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

n is 0, 1, 2 or 3; and

each R^3 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^6-R^{11}$$

wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ and $N(R^{13})C(R^{13})_2$, wherein R^{13} is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q^5 optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for any one of the 'Q' groups (Q^1 or Q^3) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (Q^1 or Q^3) when it is (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2;5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a

heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

In structural Formula I there is a hydrogen atom at the 2-position on the quinazoline ring. It is to be understood thereby that the R^1 substituents may only be located at the 5-, 6-, 7- or 8-positions on the quinazoline ring *i.e.* that the 2-position remains unsubstituted. It is further to be understood that the R^3 group that may be present on the 2,3-methylenedioxypyridyl group within structural Formula I may be located on either the 5- or 6-membered ring portions thereof, *i.e.* an R^3 group may be located on the pyridyl ring or on the methylene group within the 2,3-methylenedioxypyridyl group. Preferably, any R^3 group that is present on the 2,3-methylenedioxypyridyl group within structural Formula I is located on the pyridyl ring thereof. It is further to be understood that, when multiple R^3 groups are present, the R^3 groups may be the same or different.

Suitable values for any of the 'R' groups (R^1 to R^{13}) or for various groups within an R^1 or R^3 substituent include:-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl and ethylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl and ethylsulphonyl;
for (1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

for N,N-di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (2-6C)alkanoyl:	acetyl, propionyl and isobutyryl;
for (2-6C)alkanoyloxy:	acetoxy and propionyloxy;
for (2-6C)alkanoylamino:	acetamido and propionamido;
for N-(1-6C)alkyl-(2-6C)alkanoylamino:	N-methylacetamido and N-methylpropionamido;
for N-(1-6C)alkylsulphamoyl:	N-methylsulphamoyl and N-ethylsulphamoyl;
for N,N-di-[(1-6C)alkyl]sulphamoyl:	N,N-dimethylsulphamoyl;
for (1-6C)alkanesulphonylamino:	methanesulphonylamino and ethanesulphonylamino;
for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino:	N-methylmethanesulphonylamino and N-methylethanesulphonylamino;
for (3-6C)alkenoylamino:	acrylamido, methacrylamido and crotonamido;
for N-(1-6C)alkyl-(3-6C)alkenoylamino:	N-methylacrylamido and N-methylcrotonamido;
for (3-6C)alkynoylamino:	propiolamido;
for N-(1-6C)alkyl-(3-6C)alkynoylamino:	N-methylpropiolamido;
for amino-(1-6C)alkyl:	aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
for (1-6C)alkylamino-(1-6C)alkyl:	methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
for di-[(1-6C)alkyl]amino-(1-6C)alkyl:	dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
for halogeno-(1-6C)alkyl:	chloromethyl, 2-fluoroethyl, 2-chloroethyl, 1-chloroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3-chloropropyl, 3,3-difluoropropyl and 3,3,3-trifluoropropyl;
for hydroxy-(1-6C)alkyl:	hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
for (1-6C)alkoxy-(1-6C)alkyl:	methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
for cyano-(1-6C)alkyl:	cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and

3-cyanopropyl;

for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminoethyl.

A suitable value for $(R^1)_m$ when it is a (1-3C)alkylenedioxy group or for a R^1 substituent when it contains a (1-3C)alkylenedioxy group is, for example, methylenedioxy, ethylidenedioxy, isopropylidenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^1-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinazoline ring and the oxygen atom is attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula -X^3-Q^3 and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^3 group. A similar convention applies to the attachment of the groups of the formulae Q^2-X^2- and -X^7-Q^5.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^5)$ or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent such as a group of the formula Q^2-X^2- wherein X^2 is, for example, NHCO and Q^2 is a heterocyclyl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, suitable R^1 substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless

otherwise stated, each of Z, m, R^1, n and R^3 has any of the meanings defined hereinbefore or in paragraphs (a) to (n) hereinafter :-

(a) Z is O, S, SO, SO_2, CH_2 or NH;

(b) Z is O;

(c) Z is NH;

(d) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, N(R^4), CON(R^4), N(R^4)CO and OC(R^4)$_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, N(R^5), CON(R^5), N(R^5)CO, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl, or, when the inserted group is N(R^5), R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is CO or N(R^6)CO, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno groups or a substituent selected from hydroxy, amino, oxo, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

(2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, N(R^6), CON(R^7), N(R^7)CO and C(R^7)$_2$O, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl and (1-3C)alkylenedioxy, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and N(R^9), wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, N(R^{10}) and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(e) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, vinyl, allyl, but-3-enyl, pent-4-enyl, hex-5-enyl, ethynyl, 2-propynyl, but-3-ynyl, pent-4-ynyl, hex-5-ynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, allyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, ethynyloxy, 2-propynyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propyl, 4-(1,2,3,6-tetrahydropyridin-1-yl)butyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is CO, NHCO or N(Me)CO and Q^2 is pyridyl, pyridylmethyl, 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, oxo, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^3 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, allyl, 2-propynyl, methoxy, methylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, propionyl, isobutyryl, methylenedioxy, ethylidendioxy and isopropylidenedioxy, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and NH and R^8 is 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl,

2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, NH and CO and Q^4 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(f) m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy,

2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 is imidazolylmethyl, 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl,

2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, ethoxy, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with allyl, 2-propynyl, methylsulphonyl, ethylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(g) m is 1 and the R^1 group is located at the 7-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 6- and 7-positions and each R^1 is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy,

piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(h) m is 1 and the R^1 group is located at the 5-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions and each R^1 is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,

2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(i) m is 2 and the R^1 groups, which may be the same or different, are located at the 6- and 7-positions and the R^1 group at the 6-position is selected from hydroxy, methoxy, ethoxy and propoxy, and the R^1 group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo,

amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(j) m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions and the R^1 group at the 5-position is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the R^1 group at the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl,

piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(k) n is 0;

(l) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 5- and/or 6-positions of the 2,3-methylenedioxypyridin-4-yl group and are selected from halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;

(m) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 5- and/or 6-positions of the 2,3-methylenedioxypyridin-4-yl group and are selected from fluoro, chloro, bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, isopropenyl, ethynyl, 1-propynyl, 2-propynyl, methoxy and ethoxy; and

(n) n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group, especially the 5-position, and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy.

Further particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m, R^1, n and R^3 has any of the meanings defined hereinbefore provided that :-

(A) R^1 substituents may only be located at the 5-, 6- and/or 7-positions on the quinazoline ring *i.e.* the 2- and 8-positions remain unsubstituted; or

(B) R^1 substituents may only be located at the 6- and/or 7-positions on the quinazoline ring *i.e.* the 2-, 5- and 8-positions remain unsubstituted.

A particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is O or NH;

m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino,

ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 is imidazolylmethyl, 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, ethoxy, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with allyl, 2-propynyl, methylsulphonyl, ethylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2

substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the R^1 groups, which may be the same or different, are located at the 6- and 7-positions and the R^1 group at the 6-position is selected from hydroxy, methoxy, ethoxy and propoxy, and the R^1 group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted

with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy, 4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,

2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy; and

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl and cyano;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

n is 1 and the R^3 group is located at the 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro and bromo;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions and the R^1 group at the 5-position is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the R^1 group at the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy,

2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 1 and the R^1 group is located at the 5-position and is selected from ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, N-methylazetidin-3-yloxy, N-ethylazetidin-3-yloxy, N-isopropylazetidin-3-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy,

pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, N-(2-methoxyethyl)piperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

or m is 2 and the first R^1 group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy, 4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 1 and the R^1 group is located at the 5-position and is selected from propoxy, isopropoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

or m is 2 and the first R^1 group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy,

4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 1 and the R^1 group is located at the 5-position and is selected from propoxy, isopropoxy, tetrahydropyran-4-yloxy, 4-piperidinyloxy and N-methylpiperidin-4-yloxy,

or m is 2 and the first R^1 group is located at the 5-position and is selected from the group of substituents listed immediately above, and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl and cyano;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the first R^1 group is located at the 5-position and is selected from isopropoxy and tetrahydropyran-4-yloxy, and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

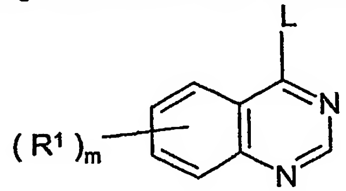
n is 1 and the R^3 group is located at the 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro and bromo;

or a pharmaceutically-acceptable acid-addition salt thereof.

Particular compounds of the invention are, for example, the quinazoline derivatives of the Formula I that are disclosed within Example 3, and Example 6(1) to 6(7) hereinafter.

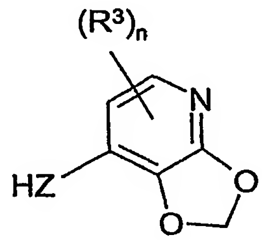
A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, m, R^1, Z, n and R^3 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) For the production of those compounds of the Formula I wherein Z is an O, S or N(R^2) group, the reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and m and R^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula III



III

wherein Z is O, S, or N(R^2) and n, R^3 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as

N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, preferably in the range 0 to 120°C.

Typically, the quinazoline of the Formula II may be reacted with a compound of the Formula III in the presence of an aprotic solvent such as N,N-dimethylformamide, conveniently in the presence of a base, for example potassium carbonate or sodium hexamethyldisilazane, and at a temperature in the range, for example, 0 to 150°C, preferably in the range, for example, 0 to 70°C.

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or

branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

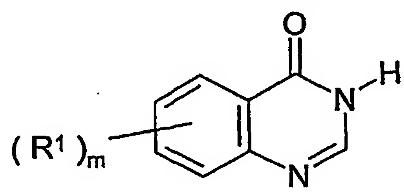
Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and

reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Quinazoline starting materials of the Formula II may be obtained by conventional procedures such as those disclosed in International Patent Applications WO 01/94341 and WO 02/16352. For example, a 1,4-dihydroquinolin-4-one of Formula IV



IV

wherein m and R^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

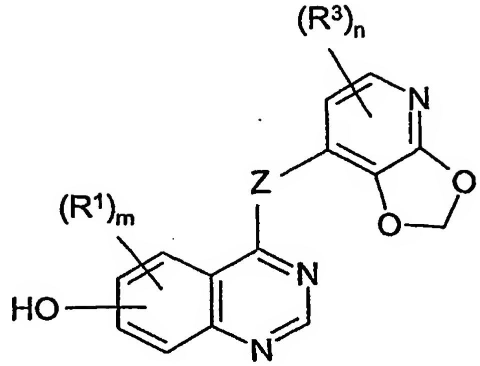
The 4-chloroquinazoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

4-Amino-2,3-methylenedioxypyridine starting materials (Formula III, for example when Z is NH) may be obtained by conventional procedures as illustrated in the Examples. Corresponding 4-hydroxy- and 4-mercapto-2,3-methylenedioxypyridine starting materials (Formula III, when Z is O or S respectively) may be obtained by conventional procedures.

(b) For the production of those compounds of the Formula I wherein at least one R^1 group is a group of the formula

$$Q^1\text{-}X^1\text{-}$$

wherein Q^1 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X^1 is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinazoline of the Formula V



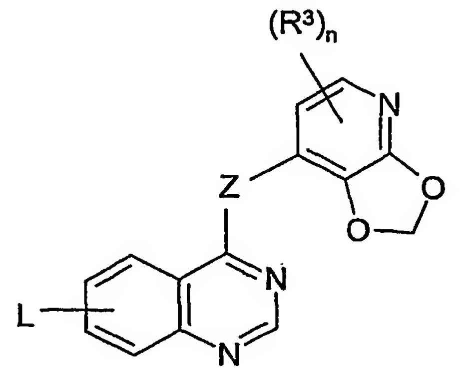
V

wherein m, R^1, Z, n and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

(c) For the production of those compounds of the Formula I wherein an R^1 group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline derivative of the Formula VI



VI

wherein L is a displaceable group as defined hereinbefore and Z, n and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an alcohol or amine as appropriate whereafter any protecting group that is present is removed by conventional means.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 50°C.

(d) For the production of those compounds of the Formula I wherein R^1 is an amino-substituted (1-6C)alkoxy group (such as a 2-(4-methylpiperazin-1-yl)ethoxy or 3-dimethylaminopropoxy group), the reaction of a compound of the Formula I wherein R^1 is a halogeno-substituted (1-6C)alkoxy group with a nitrogen-containing heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 180°C, preferably in the range 60 to 120°C.

(e) For the production of those compounds of the Formula I wherein R^1 is an amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-pyrrolidin-1-ylpropoxy or 3-[N-allyl-N-methylamino]-2-hydroxypropoxy), the reaction of a compound of the Formula I wherein the R^1 group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(f) For the production of those compounds of the Formula I wherein Z is a SO or SO_2 group, the oxidation of a compound of Formula I wherein Z is a S group.

Conventional oxidation reagents and reaction conditions for such partial or complete oxidation of a sulphur atom are well known to the organic chemist.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as c-Src tyrosine kinase inhibitors, as inhibitors in vitro of the proliferation of c-Src transfected fibroblast cells, as inhibitors in vitro of the migration of A549 human lung tumour cells and as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue.

(a) In Vitro Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional Elisa assay.

A substrate solution [100µl of a 20µg/ml solution of the polyamino acid Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum Albumin (BSA; 150µl of a 5% solution in PBS) were transferred into each substrate-coated assay well and incubated for 1 hour at ambient temperature to block non specific binding. The assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300µl/well) before being blotted dry.

Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled water to give a series of dilutions (from 100µM to 0.001µM). Portions (25µl) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells contained diluted DMSO instead of compound. Aliquots (25µl) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40µM) was added to all test wells except the "blank" control wells which contained magnesium chloride without ATP.

Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to

use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the reactions, aliquots (50μl) of freshly diluted enzyme were added to each well and the plates were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321; 100μl) was diluted by a factor of 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Catalogue No. NXA 931; 100μl) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and the wells were washed with PBST (x4).

A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue No. 1204 521). Aliquots (100μl) of the resultant solution were added to each well. The plates were incubated for 20 to 60 minutes at ambient temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) <u>In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay</u>

This assay determined the ability of a test compound to inhibit the proliferation of National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, <u>Cell</u>, 1987, <u>49</u>, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at 1.5 x 10^4 cells per well into 96-well tissue-culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium

chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20μl) were added to each well to give a final concentration of 10μM). The plates were incubated at 37°C for 2 hours. The medium was decanted. A denaturating solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50μl) was added to each well and the plates were placed on a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and the wells were washed with PBS (200μl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100μl) of the resultant solution was added to each well. The plates were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non-bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim Catalogue No. 647 229; 100μl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC_{50} value was derived.

(c) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium(Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose (Difco Catalogue No. 0142-01) was warmed to 37°C in a water bath. A stock 2% aqueous agar solution was autoclaved and stored at 42°C. An aliquot (1.5 ml) of the agar solution was added to RPMI medium (10 ml) immediately prior to its use. A549 cells (Accession No.

ATCC CCL185) were suspended at a concentration of 2 x 10^7 cells/ml in the medium and maintained at a temperature of 37°C.

A droplet (2µl) of the cell/agarose mixture was transferred by pipette into the centre of each well of a number of 96-well, flat bottomed non-tissue-culture-treated microtitre plate (Bibby Sterilin Catalogue No. 642000). The plates were placed briefly on ice to speed the gelling of the agarose-containing droplets. Aliquots (90µl) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10µl) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO_2 : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC_{50} was derived by plotting the mean migration measurement against test compound concentration.

(d) In Vivo A549 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of about 5 x 10^6 A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were prepared as a ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth was assessed.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

Test (a):- IC_{50} in the range, for example, 0.001 - 10 µM;

Test (b):- IC_{50} in the range, for example, 0.01 - 20 µM;

Test (c):- activity in the range, for example, 0.1-25 µM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day.

In general, particular compounds of the Formula I such as those provided hereinafter as Examples possess activity at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

Test (a):- IC_{50} in the range, for example, 0.001 - 0.1 μM;

Test (b):- IC_{50} in the range, for example, 0.01 - 1 μM;

Test (c):- activity in the range, for example, 0.1-1 μM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day;.

No physiologically-unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an

appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

As stated above, it is known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate cell motility which is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. We have found that the quinazoline derivatives of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

Accordingly the quinazoline derivatives of the present invention are of value as anti-tumour agents, in particular as selective inhibitors of the motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. Particularly, the quinazoline derivatives of the present invention are of value as anti-invasive agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple non-receptor

tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the enzyme c-Src, *i.e.* the compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the present invention are expected to be useful in the prevention or treatment of solid tumour disease.

Thus according to this aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases

such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory effect.

The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase

inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α-reductase such as finasteride;

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor,

approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of c-Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following Examples in which, generally :

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields, where present, are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of

300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

(viii) where certain compounds were obtained as an acid-addition salt, for example a mono hydrochloride salt or a dihydrochloride salt, the stoichiometry of the salt was based on the number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data;

(ix) the following abbreviations have been used:-

DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran
DMA	N,N-dimethylacetamide

Example 1

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline

Sodium hexamethyldisilazane (1M solution in THF; 0.734 ml) was added to a solution of 4-amino-5-chloro-2,3-methylenedioxypyridine (0.12 g) in DMF (4 ml) that had been cooled to 0°C and the mixture was stirred for 15 minutes. A portion (0.1 g) of 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline was added and the resultant mixture was stirred and allowed to warm to ambient temperature. The mixture was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent followed by increasingly polar mixtures of methylene chloride and acetonitrile. There was thus obtained the title compound as a white foam (0.11 g); NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 423 and 425.

The 4-amino-5-chloro-2,3-methylenedioxypyridine used as a starting material was prepared as follows :-

Bromochloromethane (20 ml) was added to a mixture 5-chloro-2,3-dihydroxypyridine (30 g), caesium carbonate (100 g) and DMF (300 ml) and the mixture was stirred and heated to 90°C for 3.5 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using methylene chloride as eluent. There was thus obtained 5-chloro-2,3-methylenedioxypyridine as a white solid (4.7 g); NMR Spectrum: ($DMSOd_6$) 6.25 (s, 2H), 7.5 (s, 1H), 7.65 (s, 1H).

A mixture of diisopropylamine (8.2 ml) and THF (100 ml) was cooled to -70°C and n-butyllithium (2.5 M in hexane, 24 ml) was added dropwise. The mixture was stirred at -70°C for a further 20 minutes. A solution of 5-chloro-2,3-methylenedioxypyridine (4.2 g) in THF (40 ml) was added over 10 minutes and the reaction mixture was stirred at -70°C for 1 hour. Dry carbon dioxide gas was bubbled into the reaction mixture for 30 minutes. The resultant reaction mixture was allowed to warm to ambient temperature. Water (20 ml) was added and the organic solvent was evaporated. The residue was acidified to pH2 by the

addition of 1N aqueous hydrochloric acid solution. The resultant solid was isolated and washed in turn with water and diethyl ether and dried under vacuum at 40°C. There was thus obtained 5-chloro-2,3-methylenedioxypyridine-4-carboxylic acid (3.6 g); ^{13}C NMR Spectrum: ($DMSOd_6$) 103, 120, 121, 138, 140, 158, 163.

A mixture of the material so obtained, diphenylphosphoryl azide (3.6 ml), anhydrous tert-butanol (13.5 ml), triethylamine (4.2 ml) and 1,4-dioxane (63 ml) was stirred and heated to 100°C for 3 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained tert-butyl 5-chloro-2,3-methylenedioxypyrid-4-ylcarbamate (3.8 g); NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.2 (s, 2H), 7.7 (s, 1H), 9.2 (s, 1H).

The material so obtained was dissolved in methylene chloride (35 ml) and the solution was cooled to 0°C. Trifluoroacetic acid (15 ml) was added and the mixture was stirred at 0°C for 3 hours. The mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The solvent was evaporated and the residue was diluted with ice water and neutralised to pH7 by the addition of 2N aqueous sodium hydroxide solution whilst keeping the mixture temperature at 0°C. The resultant mixture was extracted with methylene chloride and the extract dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and diethyl ether as eluent. There was thus obtained 4-amino-5-chloro-2,3-methylenedioxypyridine (2 g); NMR Spectrum: ($DMSOd_6$) 6.1 (s, 2H), 6.2 (s, 2H), 7.45 (s, 1H); ^{13}C NMR Spectrum: ($DMSOd_6$) 100, 112, 125, 136, 138, 157; Mass Spectrum: $M+H^+$ 173.

The 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

Ammonium formate (45 g) was added portionwise over 1.25 hours to a stirred mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 02/16352, Example 1 thereof; 20 g), 10% palladium-on-carbon catalyst (3.3 g) and DMF (530 ml) and the reaction mixture was stirred for an additional 30 minutes. The catalyst was removed by filtration and the solvent was evaporated. There was thus obtained 7-hydroxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.65 g); NMR Spectrum: ($DMSOd_6$) 3.9 (s, 3H), 7.0 (s, 1H), 7.45 (s, 1H), 7.9 (s, 1H).

A mixture of the material so obtained, acetic anhydride (63 ml) and pyridine (7.5 ml) was heated to 100°C for 4.5 hours. The resultant mixture was allowed to stand at ambient temperature for 16 hours. The mixture was poured into a stirred mixture (400 ml) of ice and water. The resultant precipitate was isolated and dried under vacuum. Analysis revealed that hydrolysis of the acetate group on the 4 position of the quinazoline was incomplete. The mixture was therefore further hydrolysed with water (150 ml) and pyridine (a few drops) at 90°C for 15 minutes. The resultant mixture was cooled to ambient temperature and the solid was collected by filtration, washed with water and dried under vacuum. There was thus obtained 7-acetoxy-6-methoxy-3,4-dihydroquinazolin-4-one (7.4 g); NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H), 3.9 (s, 3H), 7.45 (s, 1H), 7.65 (s, 1H), 8.05 (s, 1H).

A mixture of a portion (2 g) of the material so obtained, thionyl chloride (32 ml) and DMF (5 drops) was stirred and heated to reflux for 1.5 hours. The mixture was cooled to ambient temperature and the excess of thionyl chloride was evaporated. Toluene was added to the residue and evaporated. The resultant residue was diluted with methylene chloride (15 ml) and a 10% ammonia solution in methanol (80 ml) was added and the mixture was heated to 80°C for 10 minutes. The mixture was cooled to ambient temperature and evaporated. Water was added to the residue and the mixture was neutralised by the addition of dilute aqueous hydrochloric acid solution. The resultant precipitate was collected by filtration and dried under vacuum at 35°C for 16 hours. There was thus obtained 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g); NMR Spectrum: ($DMSOd_6$) 4.0 (s, 3H), 7.25 (s, 1H), 7.4 (s, 1H), 8.8 (s, 1H).

Di-tert-butyl azodicarboxylate (2.3 g) was added portionwise over a few minutes to a stirred mixture of 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g), 3-chloropropanol (0.7 ml), triphenylphosphine (2.6 g) and methylene chloride (100 ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The mixture was concentrated to a volume of about 30 ml by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline as a white solid (2 g); NMR Spectrum: ($DMSOd_6$) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 7.45 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

Example 2

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 92% yield; NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 4.05 (s, 3H), 4.1 (t, 2H), 4.55 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 409 and 411.

The 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

1,2-Dichloroethane (400 ml) was added to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 02/16352, Example 2, Note [4] thereof; 85 g), potassium carbonate (77 g) and DMF (400 ml) and the reaction mixture was heated to 70°C for 16 hours. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the solid so obtained was washed with water and dried over phosphorus pentoxide at 50°C. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 7-(2-chloroethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one as a white solid (65.6 g); NMR Spectrum: ($CDCl_3$) 1.2 (s, 9H), 3.9 (t, 2H), 4.0 (s, 3H), 4.4 (t, 2H), 5.95 (s, 2H), 7.1 (s, 1H), 7.7 (s, 1H), 8.2 (s, 1H); Mass Spectrum: $M+H^+$ 369 and 371.

A mixture of the material so obtained and a saturated solution of ammonia gas in methanol (1.6 L) was stirred at ambient temperature for 2 days. The solvent was concentrated by evaporation to about one-fourth of the original volume and the precipitate was collected by filtration and washed with diethyl ether. There was thus obtained 7-(2-chloroethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one as a white solid (44 g); NMR Spectrum: ($DMSOd_6$) 3.9 (s, 3H), 4.05 (t, 2H), 4.4 (t, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 255 and 257.

A mixture of a portion (5 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.7 ml) was stirred and heated to 80°C for 1.5 hours. The excess of thionyl chloride was evaporated and toluene was added and evaporated. The residual solid was suspended in a mixture of ice and water and basified to pH7.5 by the addition of 2N aqueous sodium hydroxide solution followed by a saturated aqueous sodium bicarbonate solution. The

resultant solid was collected by filtration, washed with water and diethyl ether and dried over over phosphorus pentoxide under vacuum. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and acetonitrile as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline (3.06 g; NMR Spectrum: ($CDCl_3$) 3.95 (t, 2H), 4.1 (s, 3H), 4.5 (t, 2H), 7.35 (s, 1H), 7.45 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 273 and 275.

Example 3

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline

A mixture of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline (0.08 g), 1-prop-2-ynylpiperazine (0.047 g), potassium iodide (0.01 g) and DMA (2 ml) was stirred and heated to 80°C for 3.5 hours. The solvent was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol and then a 9:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The resulting gum was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.066 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3 (m, 2H), 3.2-3.6 (br m, 10H), 3.75 (s, 1H), 3.95 (br s, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 511 and 513.

The 1-prop-2-ynylpiperazine used as a starting material was prepared as follows :-

Propargyl bromide (80% solution in toluene; 40 ml) was added dropwise during 10 minutes to a stirred mixture of 1-tert-butoxycarbonylpiperazine (50 g), potassium carbonate (74.2 g) and acetonitrile (2 L) that had been cooled to 0°C. The mixture was stirred for 1.5 hours and allowed to warm to ambient temperature. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained tert-butyl 4-prop-2-ynylpiperazine-1-carboxylate as an oil (45.5 g); NMR Spectrum: ($CDCl_3$) 1.4 (s, 9H), 2.2 (s, 1H), 2.45 (m, 4H), 3.3 (s, 2H), 3.45 (m, 4H).

A solution of the material so obtained in methylene chloride (100 ml) was added slowly to a solution of hydrogen chloride gas in 1,4-dioxane (4M, 450 ml). The reaction was

slightly exothermic and a precipitate formed as carbon dioxide gas was evolved. The mixture was stirred at ambient temperature for 1 hour. The resultant mixture was evaporated and the residue was suspended in methylene chloride. A solution of ammonia gas in methanol (7M, 110 ml) was added and the mixture was stirred at ambient temperature for 15 minutes. The mixture was filtered and the filtrate was evaporated. An oil was obtained which crystallised on standing. There was thus obtained 1-prop-2-ynylpiperazine (23 g); NMR Spectrum: ($CDCl_3$) 2.2 (s, 1H), 2.5 (br s, 4H), 2.85 (m, 4H), 3.25 (s, 2H).

Example 4

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 37% yield; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 3.65 (m, 2H), 3.9 (m, 2H), 4.1 (m, 2H), 4.4 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6.65 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 479 and 481.

The 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline used as a starting material was prepared as follows :-

Di-tert-butyl azodicarboxylate (0.338 g) was added to a stirred mixture of 4-chloro-7-hydroxy-5-tetrahydropyran-4-yloxyquinazoline (International Patent Application WO 01/94341, Example 15, Note [10] thereof; 0.25 g), 2-chloroethanol (0.073 ml), triphenylphosphine (0.385 g) and methylene chloride (15 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated to a volume of about 5 ml by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline as a solid (0.17 g); NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.15 (m, 2H), 3.7 (m, 2H), 3.95 (t, 2H), 4.1 (m, 2H), 4.4 (t, 2H), 4.8 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 8.85 (s, 1H).

Example 5

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 86% yield; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.9 (m, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.65 (s, 1H); Mass Spectrum: $M+H^+$ 437 and 439.

The 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline used as a starting material was prepared as follows :-

Di-tert-butyl azodicarboxylate (28.9 g) was added to a stirred mixture of 7-benzyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/94341, Example 15, Note [8] thereof; 30 g), isopropanol (7.3 ml), triphenylphosphine (32.95 g) and methylene chloride (350 ml) that had been cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 1.5 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 7-benzyloxy-5-isopropoxy-3,4-dihydroquinazolin-4-one as a solid (23.8 g); NMR Spectrum: ($DMSOd_6$) 7.89 (s, 1H), 7.5-7.3 (m, 5H), 6.75 (s, 1H), 6.62 (s, 1H), 5.24 (s, 2H), 4.65 (m, 1H), 1.29 (d, 6H).

Ammonium formate (48.4 g) was added to a stirred mixture of 7-benzyloxy-5-isopropoxy-3,4-dihydroquinazolin-4-one (23.8 g), 10% palladium-on-carbon catalyst (2.8 g) and DMF (300 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The mixture was filtered and the filtrate was evaporated. The material so obtained was triturated under water, the pH of which was adjusted to pH7. The solid so obtained was collected by filtration, washed with water and with diethyl ether and dried over phosphorus pentoxide under vacuum. There was thus obtained 7-hydroxy-5-isopropoxy-3,4-dihydroquinazolin-4-one as a white solid (15.9 g); NMR Spectrum: ($DMSOd_6$) 1.3 (d, 6H), 4.57 (m, 1H), 6.42 (s, 1H), 6.5 (s, 1H), 7.8 (s, 1H).

A mixture of the material so obtained, acetic anhydride (34 ml) and pyridine (0.62 ml) was heated to 70°C for 30 minutes. The reaction mixture was cooled to ambient temperature and the excess of acetic anhydride was evaporated. The white solid so obtained was added to hot water (80°C, 250 ml) and the mixture was stirred vigorously

and heated to 80°C for 20 minutes. The mixture was cooled to ambient temperature and the solid was isolated and dried over phosphorus pentoxide. There was thus obtained 7-acetoxy-5-isopropoxy-3,4-dihydroquinazolin-4-one (17.86 g); NMR Spectrum: ($DMSOd_6$) 7.97 (s, 1H), 6.91 (s, 1H), 6.85 (s, 1H), 4.65 (m, 1H), 2.32 (s, 3H), 1.33 (d, 6H).

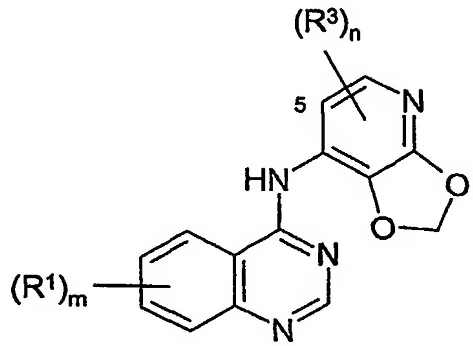
A mixture of a portion (5.4 g) of the material so obtained, triphenylphosphine (10.8 g), carbon tetrachloride (12 ml) and 1,2-dichloroethane (50 ml) was stirred and heated to 70°C for 2 hours. The mixture was cooled to ambient temperature and the solvent was evaporated. The residue was dissolved in a 0.5M solution of ammonia gas in 1,4-dioxane (250 ml) and the mixture was heated to 70°C for 10 minutes. The solvent was evaporated and the residue was cooled in an ice-water bath. Methylene chloride and water were added and the aqueous layer was brought to pH7 by the addition of dilute aqueous hydrochloric acid. The mixture was filtered. The organic phase was dried over magnesium sulphate and evaporated to give 4-chloro-7-hydroxy-5-isopropoxyquinazoline as a foam which was used without further purification.

Di-tert-butyl azodicarboxylate (7.9 g) was added to a stirred mixture of the 4-chloro-7-hydroxy-5-isopropoxyquinazoline so obtained, 2-chloroethanol (1.5 ml), triphenylphosphine (8 g) and methylene chloride (200 ml) and the reaction mixture was stirred at ambient temperature for 4 hours. The mixture was concentrated by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline (2.5 g); NMR Spectrum: ($CDCl_3$) 1.45 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.75 (m, 1H), 6.65 (s, 1H), 6.9 (s, 1H), 8.8 (s, 1H).

Example 6

Using an analogous procedure to that described in Example 3, the appropriate 7-haloalkoxyquinazoline was reacted with the appropriate heterocyclic compound to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a free base.

Table I



Compound No. & Note	$(R^1)_m$	$(R^3)_n$
[1]	6-methoxy-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]	5-chloro
[2]	6-methoxy-7-{3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy}	5-chloro
[3]	6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]	5-chloro
[4]	5-tetrahydropyran-4-yloxy-7-[2-(4-acetylpiperazin-1-yl)ethoxy]	5-chloro
[5]	5-tetrahydropyran-4-yloxy-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}	5-chloro
[6]	5-isopropoxy-7-[2-(4-acetylpiperazin-1-yl)ethoxy]	5-chloro
[7]	5-isopropoxy-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}	5-chloro

Notes

[1] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline and 1-isobutyrylpiperazine. The reaction mixture was heated to 120°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The material so obtained was dissolved in methylene chloride and an ion exchange resin (diethylaminopolystyrene resin, 4 equivalents) was added and the mixture was stirred for 30 minutes. The mixture was filtered and the filtrate was evaporated. The resultant residue was triturated under pentane to

give the required product in 51% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.1 (d, 6H), 2.1 (m, 2H), 2.45 (m, 4H), 2.55 (m, 2H), 2.75 (m, 1H), 3.5 (m, 2H), 3.6 (m, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (br s, 1H); Mass Spectrum: $M+H^+$ 543 and 545.

The 1-isobutyrylpiperazine used as a starting material was prepared as follows :-

Isobutyryl chloride (3.25 ml) was added dropwise to a stirred mixture of 1-benzylpiperazine (5 g), triethylamine (4.35 ml) and methylene chloride (75 ml) which was cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 1-benzyl-4-isobutyrylpiperazine (5.95 g) as an oil; NMR Spectrum: ($CDCl_3$) 1.1 (d, 6H), 2.45 (m, 4H), 2.8 (m, 1H), 3.5 (m, 4H), 3.65 (m, 2H), 7.3 (m, 5H); Mass Spectrum: $M+H^+$ 247.

A mixture of the material so obtained, cyclohexene (70 ml), palladium oxide-on-carbon catalyst (20%; 1.1 g) and ethanol (120 ml) was stirred and heated to 80°C for 3 hours. The catalyst was removed by filtration and the solvent was evaporated to give 1-isobutyrylpiperazine (3.7 g) as a solid; NMR Spectrum: ($CDCl_3$) 1.05 (d, 6H), 2.75 (m, 1H), 2.8 (m, 4H), 3.45 (m, 2H), 3.55 (m, 2H).

[2] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline and 1-(2,2,2-trifluoroethyl)piperazine. The reaction mixture was heated to 120°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The material so obtained was dissolved in methylene chloride and an ion exchange resin (diethylaminopolystyrene resin, 4 equivalents) was added and the mixture was stirred for 30 minutes. The mixture was filtered and the filtrate was evaporated. The resultant residue was triturated under pentane to give the required product in 72% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.5 (m, 6H), 2.7 (m, 4H), 2.95 (q, 2H), 4.05 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.35 (br s, 1H); Mass Spectrum: $M+H^+$ 555 and 557; Elemental Analysis: Found C, 51.8; H, 5.0; N, 14.8; $C_{24}H_{26}ClF_3N_6O_4$ requires C, 51.9; H, 4.7; N, 15.1%.

The 1-(2,2,2-trifluoroethyl)piperazine used as a starting material was prepared as follows :-

2,2,2-Trifluoroethyl trifluoromethanesulphonate (8.2 g) was added to a stirred mixture of 1-tert-butoxycarbonylpiperazine (6 g), potassium carbonate (5.77 g) and acetonitrile (30 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl 4-(2,2,2-trifluoroethylpiperazine-1-carboxylate as a solid (8.1 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.6 (m, 4H), 2.95 (q, 2H), 3.4 (m, 4H).

Hydrogen chloride gas was bubbled through a solution of tert-butyl 4-(2,2,2-trifluoroethylpiperazine-1-carboxylate (8 g) in ethyl acetate (50 ml) during 1.5 hours. A precipitate formed as carbon dioxide gas was evolved. The precipitate was collected by filtration, washed with ethyl acetate and dried under vacuum. There was thus obtained 1-(2,2,2-trifluoroethyl)piperazine hydrochloride (7 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.85 (m, 4H), 3.1 (m, 4H), 3.35 (q, 2H).

The material so obtained was suspended in methylene chloride and a saturated methanolic ammonia solution (20 ml) was added. The resultant mixture was stirred at ambient temperature for 20 minutes. The mixture was filtered and the filtrate was evaporated at ambient temperature under vacuum. There was thus obtained 1-(2,2,2-trifluoroethyl)piperazine which was used without any additional purification.

[3] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline and 1-prop-2-ynylpiperazine. The required product was obtained in 52% yield and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 3.3 (br s, 4H), 3.6 (br s, 4H), 3.75 (br s, 3H), 3.95 (s, 2H), 4.05 (s, 3H), 4.65 (t, 2H), 6.3 (s, 2H), 7.5 (s, 1H), 7.9 (s, 1H), 8.2 (s, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 497 and 499; Elemental Analysis: Found C, 56.3; H, 5.4; N, 16.2; $C_{24}H_{25}ClN_6O_4$ $0.7H_2O$ requires C, 56.6; H, 5.2; N, 16.5%.

[4] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 80°C for 3 hours and then to 110°C for 5 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly

polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7.5. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 45% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.1 (s, 3H), 2.3 (m, 2H), 2.6 (m, 4H), 2.95 (m, 2H), 3.55 (m, 2H), 3.65 (m, 4H), 4.1 (m, 2H), 4.3 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 571 and 573; Elemental Analysis: Found C, 55.3; H, 5.4; N, 13.9; $C_{27}H_{31}ClN_6O_6$ $1H_2O$ requires C, 55.1; H, 5.7; N, 14.3.

[5] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 80°C for 3 hours and then to 110°C for 5 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7.5. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 69% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 2.4 (m, 2H), 2.3 (t, 2H), 3.3 (d, 2H), 3.55 (m, 2H), 4.1 (m, 2H), 4.3 (t, 2H), 4.65 (m, 2H), 4.8 (m, 1H), 4.9 (s, 1H), 5.2 (s, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 558 and 560; Elemental Analysis: Found C, 56.5; H, 5.3; N, 12.5; $C_{26}H_{28}ClN_5O_7$ $0.2Et_2O$ requires C, 56.2; H, 5.3; N, 12.2%.

The (3RS,4SR)-3,4-methylenedioxypyrrolidine used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (Boc_2O, 78.95 g) in ethyl acetate (125 ml) was added dropwise to a stirred mixture of 3-pyrroline (25 g; 65% pure containing pyrrolidine) and ethyl acetate (125 ml) which had been cooled to 0°C. The reaction temperature was maintained at 5-10°C during the addition. The resultant reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was washed successively with water, 0.1N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate

and evaporated. There was thus obtained, as a colorless oil (62 g), a 2:1 mixture of tert-butyl 3-pyrroline-1-carboxylate, NMR: ($CDCl_3$) 1.45 (s, 9H), 4.1 (d, 4H), 6.75 (m, 2H), and tert-butyl pyrrolidine-1-carboxylate, NMR: ($CDCl_3$) 1.5 (s, 9H), 1.8 (br s, 4H), 3.3 (br s, 4H).

A solution of the mixture of materials so obtained in acetone (500 ml) was added dropwise to a mixture of N-methylmorpholine-N-oxide (28.45 g), osmium tetroxide (1 g) and water (500 ml) whilst keeping the reaction temperature below 25°C. The reaction mixture was then stirred at ambient temperature for 5 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent and by further column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol. There was thus obtained tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate as an oil (34.6 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.65 (m, 2H), 3.35 (m, 2H), 3.6 (m, 2H), 4.25 (m, 2H).

A solution of tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate (34.6 g) in DMF (400 ml) was cooled to 0-5°C and sodium hydride (60% dispersion in mineral oil, 0.375 mol) was added portionwise. The reaction mixture was stirred at 5°C for 1 hour. Dibromomethane (15.6 ml) was added and the reaction mixture was stirred at 5°C for 30 minutes. The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The DMF was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate as a colourless oil (19.77 g);NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 3.35 (m, 2H), 3.75 (br s, 2H), 4.65 (m, 2H), 4.9 (s, 1H), 5.1 (s, 1H).

A cooled 5M solution of hydrogen chloride in isopropanol (150 ml) was added to a solution of tert-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate (19.7 g) in methylene chloride (500 ml) that was cooled in an ice bath. The reaction mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The solvent was evaporated and the residue was triturated under diethyl ether. The precipitate was collected by filtration, washed with diethyl ether and dried. There was thus obtained (3RS,4SR)-3,4-

methylenedioxypyrrolidine hydrochloride as a beige solid (13.18 g); NMR Spectrum: ($DMSOd_6$) 3.15 (m, 2H), 3.35 (m, 2H), 4.65 (s, 1H), 4.8 (m, 2H), 5.1 (s, 1H).

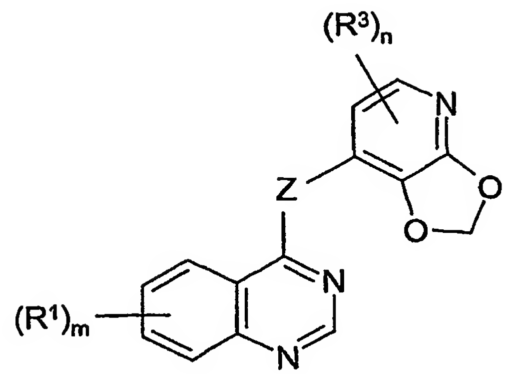
The material so obtained was suspended in diethyl ether and a saturated methanolic ammonia solution was added. The resultant mixture was stirred at ambient temperature for 10 minutes. The mixture was filtered and the solvent was evaporated at ambient temperature under vacuum. There was thus obtained (3RS,4SR)-3,4-methylenedioxypyrrolidine which was used without any additional purification.

[6] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 85°C for 8 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The product was obtained in 89% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.1 (s, 3H), 2.6 (m, 4H), 2.9 (t, 2H), 3.5 (t, 2H), 3.7 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 529 and 531; Elemental Analysis: Found C, 57.0; H, 5.71; N, 15.7; $C_{25}H_{29}ClN_6O_5$ requires C, 56.8; H, 5.5; N, 15.9%.

[7] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 95°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 64% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.35 (m, 2H), 2.9 (t, 2H), 3.25 (d, 2H), 4.25 (t, 2H), 4.6 (m, 2H), 4.85 (m, 1H), 4.9 (s, 1H), 5.15 (s, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 516 and 518; Elemental Analysis: Found C, 54.7; H, 5.2; N, 13.2; $C_{24}H_{26}ClN_5O_6$ $0.5H_2O$ requires C, 54.9; H, 5.2; N, 13.3%.

CLAIMS

1. A quinazoline derivative of the Formula I



I

wherein each of Z, m, R^1, n and R^3 have any of the meanings defined hereinbefore in the description.

2. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises any one of the process variants (a) to (f) defined hereinbefore in the description.

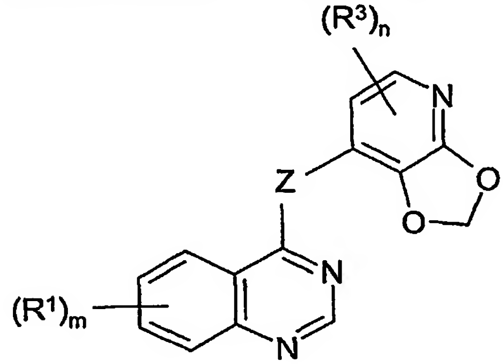
3. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

4. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

ABSTRACT

TITLE : QUINAZOLINE DERIVATIVES

The invention concerns quinazoline derivatives of Formula I



I

wherein each of Z, m, R^1, n and R^3 have any of the meanings defined hereinbefore in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

PCT Application

GB0304703

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